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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,491	12/27/2001	Shuyuan Zhang	29853/37706	9920

7590 10/07/2008

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
10/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/033,491	ZHANG ET AL.	
	Examiner	Art Unit	
	ROBERT M. KELLY	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/13/07;2/14/08;2/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Pall WebSite*.

Continuation of Disposition of Claims: Claims pending in the application are 70,71,74-78,80-83,85-102,105-114,116-134,136-145,147-165,167-176,178-195,198-207 and 209-226.

Continuation of Disposition of Claims: Claims rejected are 70,71,74-78,80-83,85-102,105-114,116-134,136-145,147-165,167-176,178-195,198-207 and 209-226.

DETAILED ACTION

Claims 70, 101, 132, 134, 163, 165, and 194 are amended.

Claims 72, 73, 84, 103, 104, 115, 135, 146, 166, 177, 196, 197, and 208 are cancelled.

Claims 70, 71, 74-78, 80-83, 85-102, 105-114, 116-134, 136-145, 147-165, 167-176, 178-195, 198-207, and 209-226 are presently pending and considered.

Claim Status, Cancelled Claims

For clarity of record, it is noted that: In light of the cancellation of Claims 72, 73, 84, 103, 104, 115, 135, 146, 166, 177, 196, 197, and 208, all rejections and/or objections to such claims are withdrawn, as they are now moot.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 70, 71, 74-78, 80-83, 85-102, 105-114, 116-134, 136-145, 147-165, 167-176, 178-195, 198-207, and 209-226 remain provisionally rejected under the judicially created

doctrine of obviousness-type double patenting as being unpatentable over claims 13-28, 31, and 33-37 of copending Application No. 09/203,078, for reasons of record.

Double-Patenting over 09/203,078 held in Abeyance

In accord with Applicant's request, the provisional double-patenting rejection over U.S. Application No. 09/203,078 is maintained, but remain held in abeyance (Applicant's response of 6/12/06, p. 30).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 70, 71, 74-78, 80-83, 85-102, 105-114, 116-134, 136-145, 147-165, 167-176, 178-195, 198-207, and 209-226 are newly provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-28, 31, and 33-37 of copending Application No. 10/033,571.

The distinction between the claims are that the other application is drawn to method of making adenovirus, however, the specifications are identical, both being derived, by continuation applications all the way back to the same provisional application, teaching the same use of such-

made adenovirus for the purpose of therapy, and with the same transgenes. Hence, in light of the Claims and specification of the 10/033,571 Application, it would be obvious to make the present invention. Such is because the purpose of making adenoviruses, with coextensive methods of making with the present claims, is for therapy. Moreover, the Artisan would have a reasonable expectation of success, as each application teaches such.

It is noted that Applicant has paid the fee for references taken from this Application, and hence, the rejection does not preclude finality. However, it is also noted that Applicant failed to make the Examiner aware of such subject matter after the initial official action. Applicant is requested to provide the Examiner with any other Applications which are drawn to similar subject matter and may require double patenting, to avoid delays in finding patentable subject matter.

Claim Rejections - 35 USC § 112 – New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 78, 109, 140, 171, and 202 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims encompass the

limitation that the adenoviral composition be "essentially free of BSA". The specification's implicit support for such limitation on page 72, paragraph 2, where it says that the compositions should be essentially free of pyrogens as well as other impurities that could be harmful to humans or animals, as well generally monitoring the level of BSA in several characterizations of technique combinations used in the examples. However, such does not equate to the scope Applicant claims, and the Examiner has only found implicit support for such limitation, in the form of a specific method which produces BSA levels below the detection limit of a western blot assay (EXAMPLE 6), hence, outside of the specific embodiment of making the virus in EXAMPLE 6, Applicant has no support for the wide breadth claimed.

Response to Argument – New Matter

Applicant's response of 2/25/08 has been fully considered but is not found persuasive.

Applicant argues that Example 6 provides sufficient support to overcome the rejection, then cites the specification for fears of Bovine Spongiform Encephalovirus being transmitted as a contaminant, then points to the use of serum-free media being stated as used and having a fetal bovine serum level lower than 0.03% v/v, wherein it is optimal to not to have pyrogens or other impurities, thereby implying that the Artisan was concerned specifically with BSA, and not BSE or other impurities. Then Applicant reviews the specification's discussion of the example, to implicate even further support, though it is really the same support as in Example 6. Then Applicant sums up to state that the bovine proteins are dangerous, the compositions should be essentially free of pyrogens and other impurities, and a demonstration of BSA detection being low in certain embodiments (when using serum-free media, and as a monitored contaminant, in certain purificaiton steps).

The Examiner understands that Applicant wishes to remove all contaminants, such is the goal of any purification, and there can be no question that Applicant wishes to remove all contaminants, but the explicit demonstration of examples, and the explicit statement of wishing to remove all pyrogens and other impurities, simply demonstrates, at best, that Applicant was wishing to monitor contaminant level in general by measuring BSA levels, not that they specifically contemplated BSA removal as a generic result of a generic method. The question essentially lies in when does implicit demonstration of something in the examples demonstrate that such was the possessed goal. At this point, given the generic methods and the lack of explicit statement that it is the goal to remove BSA, and the simple statement that all impurities are desired to be removed, the Examiner simply cannot go any further than to state that the methods are not possessed as claimed, as there is no specific contemplation in the specification as filed.

Claim Rejections - 35 USC § 112 – new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70, 71, 74-78, 80-83, 85-102, 105-114, 116-134, 136-145, 147-165, 167-176, 178-195, 198-207, and 209-226 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for comprising new matter. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The presently recited claims have the newly presented limitation "formulating said therapeutic adenovirus to provide a therapeutic adenovirus composition which has a contaminating nucleic acid content of less than 400 pg per [10^10] pfu of virus and greater than or equal to about 60 pg per [10^10] pfu of virus".

Applicant points to the examples for support for such generically claimed result, specifically to TABLE 10. Table 10, in addition to not providing anything but contaminating nucleic acid levels, fails to provide the pfu of virus at each step, and also fails to demonstrate 400 pg at all, while only providing 60 pg/mL, and not as a function of pfu. Moreover, how this equates to a generic method which will yield this result, how a specific demonstration of "60" equates to "about 60", and how concentrations relate to pg/pfu in such a matter that the Artisan would determine Applicant to have been in possession of such is beyond the ability of the Examiner to determine.

Applicant is reminded that it is their duty to demonstrate possession. At best, Applicant's implicit disclosure provides support for the specific methods and materials used in the method, not for the generic embodiments claimed.

I. Obviousness Rejections Based on 293 Cells in Serum-Free Mediums

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 70, 71, 74-78, 80-83, 85-102, 105-114, 116-134, 136-145, 147-165, 167-176, 178-195, 198-207, and 209-226 are now rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, and Berg, et al. (1993) Biotechniques, 14(6): 972-8, for reasons of record, and now further in view of the knowledge of the Artisan as evidenced by the attached Pall Website, and US Pat Nos: 6,881,552 and 5,772,888.

Note: This is a two-way rejection, applying the Art is slightly distinct manners. The distinct aspects of the first rejection are the use of 293 cells in the media of Perrin, and the distinct aspects of the second rejection are the use of 293 cells in the media of Berg.

With regard to Claims 70, 71, 74-78, 80-83, 85-102, 105-114, 116-134, 136-145, 147-165, 167-176, 178-195, 198-207, and 209-226, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.), particularly serotype 5 adenoviral vectors (e.g., EXAMPLE 2) comprising the CMV-MIE promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells (cells comprising an E1A/E1B region) (e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Moreover, these compositions are essentially free

of BSA, and below the level of a western blot assay, as the compositions are grown in the absence of BSA (e.g., EXAMPLE 2). Lastly, such compositions are administered in a pharmaceutically-acceptable buffers (e.g., col. 5, lines 1-14), which requires formulation (Id.).

With regard to exogenous coding regions for p53 operatively linked to the CMV-IE promoter (e.g., Claims 85-90), Zhang teaches such (e.g., col. 4, last paragraph).

With regard to vectors missing parts of E1A and/or E1B (e.g., Claims 91-93), Zhang teaches such (col. 4, paragraphs 2-3).

With regard to 293 host cells, which compliment the production of replication incompetent virus (e.g., Claims 94-95), Zhang teaches such (col. 4, paragraph 4)

With regard to the unit dosages and treating a patient with cancer (e.g., Claims 98-100), Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging). Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7). Therefore, Zhang inherently teaches Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

Still further, of importance to the arguments to this rejection, is the recognition by Zhang that several methods of infecting (including transfection of DNA by CaPO4 coprecipitation and liposomal transfection) may be used to transform these cells (e.g., EXAMPLE 2).

With regard to all the claims subject to this rejection, Zhang does not explicitly review the general techniques used in the art on how to manufacture the adenoviruses, specifically in importance are those through the steps of growing host cells in a media, providing nutrients to

the host cells, infecting the host cells with adenovirus, lysing said host cells, and purifying adenovirus from the lysate; although Zhang does evidence use of CsCl gradients for purification and formulation (col. 5, paragraph 1). Moreover, the other steps are inherent in Zhang, as these are required steps for growing adenovirus for use. Huyghe evidences these aspects, as Huyghe demonstrates a standard method of making such adenoviruses, in comparison to alternative methods where chromatography substitutes for CsCl centrifugation (TITLE; pp.1407-1408). Specifically, Huyghe teaches that 293 cells are infected with adenovirus vector 2.5 days after growing host cells in media, which provides the nutrients needed to grow, as well as grow adenovirus (p. 1404, col. 1, paragraph 5); cells are lysed to yield adenovirus (Id., last paragraph), and may be purified by cesium chloride (p. 1404, col. 2-1405, col. 1). Moreover, absent to believe otherwise, such produced adenovirus is essentially pure and contains BSA levels below the detection limit of a western blot assay, and is further essentially free of BSA.

With regard to methods that yield substantially pure adenoviral compositions that may be as high as 60-80% , (e.g., Claims 71-72), Huyghe teaches such, which depends on the steps utilized (p. 1408, col. 1, paragraph 2). Hence artisan would be motivated to modify the methods by using different steps and techniques in combination to obtain higher purity.

With regard to the required A260/280 ratios (e.g., Claims 75-77), as has been demonstrated above, the required levels of contaminating nucleic acid are attained in CsCl gradient isolations, and Huyghe teaches that such CsCl gradient purifications yield an AD260/280 of between 1.2-1.3, and reflects variability in the method, which indicates that individual experiments will yield 1.27.

With regard to fed batch processes (e.g., Claim 83), Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5).

With regard to treating the compositions with nucleases and the required levels of contaminating nucleic acid in the compositions (e.g., Claims 73-74, 77, and 96) Huyghe teaches treating the lysate with nuclease (p. 1404, col. 2, paragraph 2), which Applicant demonstrates achieves the required levels of nucleic acid contamination (e.g., TABLE 10).

With regard to BSA levels (All claims, and 70 and 78 in particular), although the Art utilized does not comment on BSA levels in the compositions produced, absent reason to believe otherwise the amount of BSA present is assumed to be under the levels of detection by a western blot assay, and the compositions are assumed to be essentially free of BSA.

However, Zhang does not teach the aspects of serum free media (which also further addresses the levels of BSA as none will be present in serum-free media), bioreactors, microcarriers, and perfusion methods.

On the other hand, Perrin teaches the use of serum-free media, which the Artisan is motivated to use in the manufacture of biopharmaceuticals in order to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by the use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers (Claims 80-81), Perrin teaches that it was standard practice in the art to use such bioreactors with microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (Claims 82 and 84) (Id.). Further, of importance to the arguments to this rejection is a

demonstration that the Artisan understood that the virus vector could be transformed into the cell by standard viral infection routes (p. 1246, col. 1).

Still further, it was known in the Art that at the time of invention, that the 293 cells of Zhang could be adapted to survive and grow in serum-free media and manufacture biopharmaceuticals (e.g., Berg, et al. (1993) Biotechniques, 14(6): 972-78, ABSTRACT).

Hence, from the confluence of the art provided, the Artisan recognized that there were many methods of growing, providing nutrients, infecting host cells, lysing host cells, purifying adenovirus, and formulating such purified composition to achieve the various required levels of contaminants, etc., as required by the various claims. Hence, the Artisan at the time of invention would have found it obvious to perform the methods using 293 grown in either the serum-free media of Perrin or the serum-free media of Berg.

However, the reader may still question whether or not 293 cells could grow on the serum-free media of Perrin. However, it is noted that Perrin specifically states that several cell types tested were similarly able to grow in the same medium, and no cell line has been reported which will not grow in this medium (e.g., p. 1247, last paragraph). Still further, 293 cells, as shown by Berg, were already known to be able to grow on serum-free media. Moreover, the Artisan would note that both BHK-21 and 293 cells are kidney cell types. Hence, given the absence of negative teachings, the similarity of cell type, and number of cells adapted to work in this medium, coupled with no finding of any cell type which didn't work and no teaching that other cell types would not work, the Artisan would reasonably expect that 293 cells would grow in this medium.

Furthermore, given the sheer number of separation processes available to the Artisan, and the knowledge of the Artisan with regard to processes repetition and/or phase size adjustments,

the Artisan would find it obvious to obtain any level of purity. To wit, any separation takes place as achieving an equilibrium between two phases, which are then separated. The equilibrium, being higher for one component than the other (e.g., virus particle versus nucleic acid), would pull out more of that component than the other, when separated. Then, by re-performing such process, and/or by increasing the volume of the phase which is to be removed, the amount of contaminant removed is increased relative to that of the desired product. The only problem with this is that in cases where the phase separation is very poor to start, where great losses of the desired product are also lost. However, in such cases, making more desired product to begin with allows for such loss. Hence, within the routine experimentation, any level of purity can be obtained. Such logic is one of "water is wet", and hence it has been difficult for the Examiner to find a reference teaching such basic purification procedure theory, however, the result, e.g., desire to re-perform separations, is shown as present in the prior art (e.g., US PAT NO 5,772,888 to Liu et al., Section Labelled "Multi-Stage Partitioning Operation"; and US PAT NO 4,539,020, to Sakraya, et al., which throughout teaches that the separation steps are repeated to obtain the pure component desired).

Hence, at the time of invention by Applicant, the Artisan would have found it obvious to perform the various methods, using the 293 cells of Zhang or Berg, either in the serum-free medium of (i) Perrin or (ii) Berg. The Artisan would have been motivated to do so as both Zhang and Berg teach several reasons to motivate the Artisan to use serum-free media. Moreover, the Artisan would have had a reasonable expectation of success for such methods as 293 cells had been shown to grow in serum-free media, were well known to grow adenoviral

vectors, and to be able to produce recombinant pharmaceutical proteins, which is the same as the cell being transformed by the adenovirus to produce the adenoviral proteins to grow adenovirus.

Response to Argument – all obviousness rejections

Applicant's response of 2/25/08 has been fully considered but is not found persuasive.

Applicant argues that the references do not teach or make obvious all of the limitations, specifically referring to the limitation of purity levels (pp. 24-25).

Such is not persuasive. The Art is in the purification of viruses, and Applicant is simply claiming the level of purity they obtained. Just because the Artisan did not report such level range does not mean that the Artisan would not find it obvious to obtain any particular level of purity. If the Examiner were to accept Applicant's argument, he would be arguing that the Artisan did not believe the Artisan could obtain such levels of purity. If such were the case, then Applicant would be limited to the range of specific steps which could reasonably predict such level of purity. However, even Applicant believes, according to claim language, not requiring any step, but a generic "purifying" step, that any particular combination of steps could obtain the level of purity described, and it is not undue experimentation to find those. Moreover, as is cited above, the Artisan also believed the same.

Applicant argues that Huyghe would not obtain the level of purity desired, as the pH of the lysate was too high, and purity in the range of Applicant's is not cited (pp. 25-26).

Such is not persuasive. It is well within the Artisan's grasp to read the instructions that come with the benzonase and to then optimize the pH, as well as to simply optimize the conditions of reache. Moreover, Applicant's own specification fails to describe the import of the pH optimization when such benzonase treatment is being performed. Hence, it would appear

that even Applicant understood that the Artisan knew how to read instructions, as well as pH optimization of reactions. Further, with regard to the absence of statement to the purity, the Artisan is one who purifies virus, therefore, any particular viral purity is obvious, absent reason to believe it could not exist. However, there is nothing in the Art stating that such levels of purity exist.

Applicant argues that Huyghe does not teach fed batch processes (p. 26, paragraph 2).

Such is not persuasive. Huyghe teaches feeding the batch, and given its broadest reasonable interpretation, the Artisan would therefore find such to encompass Applicant's claim language. Furthermore, to the now-intended distinction Applicant appears to be trying to make: Applicant did not invent fed-batch processes, they were known before Applicant's disclosure, otherwise, Applicant would have had to describe the "process", however, Applicant's description appears to acknowledge that such was known in the Art (e.g., paragraphs 90-91 of the specification). To argue that the Artisan did not understand Huyghe as performing a similar or the same process, and further argue that the Artisan would not find it instantly obvious, appears to be completely incorrect. Lastly, Applicant's own description of fed-batch processes, is seen to include the providing of key nutrients to the batch (e.g., paragraphs 90 and 91 of the specification), to delay decline phases, so even under such minimal description, the description of Huyghe appears to meet the limitations.

II. Obviousness Rejections Based on BHK-21 Cells in Serum-Free Media

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 70-78 and 80-90, 96-121, 127-152, 158-183, 189-214, and 220-226 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, and in view of the knowledge of the Artisan as evidenced by the attached Pall Website, and US Pat Nos: 6,881,552 and 5,772,888, as further evidenced by Rowe, et al. (1981) J. Virol. 38(1): 191-97.

These rejections are made on the same bases as above, but using the BHK-21 cells of Perrin to grow adenovirus vectors in the serum-free media of Perrin.

The distinct difference here is that the BHK-21 cells are not the 293 cells demonstrated by Zhang to grow adenovirus, and hence, the reader may argue that it was not known if BHK-21 cells could grow adenovirus. However, it was well known in the Art that the adenovirus type 5 of Zhang could be grown in BHK-21 cells at the time of invention. For Example, Rowe teaches that such viruses were known to grow in BHK-21 cells (e.g., ABSTRACT), and hence, the Artisan knew that these cells supported the growth of adenovirus serotype 5.

Still further, with regard to the various distinctions in the claims for various requirements of steps and results, the Examiner relies on the same basis as previous rejections. Essentially, these techniques were all already known in the Art for growing, lysing, and purifying cells, and the Artisan would therefore be motivated to use any particular combination of them, depending on the desired results.

Hence, at the time of invention by Applicant, the Artisan would have been motivated to use perform the various methods claimed, utilizing Ad5 cells grown in the BHK-21 cells of Perrin within the serum-free medium of Perrin. The Artisan would have been motivated to do so in order to produce virus in absence of serum, as taught by Perrin. Moreover, the Artisan would have had a reasonable expectation of success, as Perrin had taught BHK-21 cells could grow in serum free media, and further grow virus in such media, and Rowe evidenced that the Artisan already knew that BHK-21 cells supported growth of an adenovirus of Rowe.

Response to Argument – 103 BHK-21 in Serum Free Media

Applicant's argument of 2/25/08 has been fully considered but is not found persuasive.

Applicant argues that Rowe does not overcome the deficiencies of the base references (p. 26, paragraph 3).

Such is not persuasive. The further evidence provided of the skill of the Artisan demonstrates that it would still be obvious.

III. Obviousness Rejections Based on Culture Systems with Horse Serum

Claims 101, 102, 105-109, 111-114, 116-134, 136-140, 142-145, 147-165, 167-171, 173-176, 178-195, 198-202, 204-207, and 209-226 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and as evidenced by Perrin, et al. (1995) Vaccine, 13(13): 1244-50, for reasons of record, and now further in view of the knowledge of the Artisan as evidenced by the attached Pall Website, and US Pat Nos: 6,881,552 and 5,772,888, as applied to the various aspects not requiring the serum-free media of obviousness rejections of Title I, above.

The subject claims are also rejected under the same bases as Title I., above, however, not utilizing the serum-free medium or cells of Perrin, but only relying on Perrin for the other aspects of the rejection, e.g., bioreactors, microcarriers, and roller bottles.

It is noted that Zhang teaches growing the adenovirus in cells on horse-serum supplemented medium, and hence, absent reason to believe otherwise, this medium contains no BSA (bovine serum albumin). Hence, absent to believe otherwise, the obtained virus particles would not contain BSA, and would necessarily be below the level of a western blot assay.

Hence, at the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the steps of culturing, feeding, etc., of Perrin, to grow the cells in 293 cells in horse-serum supplemented medium. The Artisan would have been motivated to do so because such methods were known and standard in the Art, and absent reason to believe otherwise, the derived compositions would be BSA free. Moreover, the Artisan would have had a reasonable expectation of success as the virus had already been grown in the absence of BSA, and Perrin's techniques were well known in the art.

Response to Argument – 103, Horse Serum

Applicant's argument of 2/25/08 has been fully considered but is not found persuasive.

Applicant argues that Zhang does not overcome the deficiencies in the Art of Perrin and Huyghe, and hence, the rejection should be withdrawn (p. 26, penultimate paragraph).

Such is not persuasive. The further art demonstrating the skill of the Artisan demonstrates that the Artisan was capable of performing, in addition to the distinct combinations demonstrated previously, that the Artisan can adjust the phase separation parameters and further repeat processes to increase purity. Hence, the Artisan would still find it obvious.

IV. Further Obviousness Rejections Based on NA Levels Below 0.2ng/mL

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 74, 105, 136, 167, and 198 are further rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, and in view of the knowledge of the Artisan as evidenced by the attached Pall Website, and US Pat Nos: 6,881,552 and 5,772,888, and optionally Berg, et al. (1993) Biotechniques, 14(6): 972-79, and optionally evidenced by Rowe, et al. (1994) J. Virology, 38(1): 191-97, as applied to claims 70, 101, 132,

163, and 194, respectively above, and as further evidenced by Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11 (I.e., these claims are further rejected on the bases of I-III above, as well as the further addition of Nadeau and Trepanier.)

As is shown above, Zhang as evidenced by Huyghe and Perrin and optionally Berg, as optionally evidenced by Rowe make obvious the various aspects of claims 70, 101, 132, 163, and 194 in several manners, as shown in Titles I-III, above; however, they do not specifically discuss obtaining nucleic acid contaminations less than 0.2ng/mL, and hence, the reader may argue that the Artisan would not have expected to obtain such levels of contamination.

On the other hand, the other two references (Nadeau and Trepanier) each teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art for purification. Moreover, Applicant's specification makes clear that such ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration step would necessarily yield the desired levels of contaminating nucleic acid.

Alternatively, any particular dilution and concentration of the bulk solution would yield the level of nucleic acid claimed.

At the time of invention by Applicant it would have been obvious to modify the methods of Titles I-III, above, by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Response to Argument – Addition of Nadeau and Trepanier

Applicant's argument of 2/25/08 has been fully considered but is not found persuasive.

Applicant argues that Nadeau teaches the separation of adenovirus from the desired protein, and the purification of adenovirus, and hence, the Artisan would not find Nadeau to be relevant (p. 27, paragraphs 1-2).

Such is not persuasive. It simply does not matter which fraction you decide to keep, separation is separation.

Applicant argues that Trepanier does not teach adenoviral purification, but is instead to RSV (p. 27, last paragraph).

Such is not persuasive. The Artisan would be able to apply knowledge from analogous art, such is what the holding of KSR v. Teleflex is all about. Further, Nadeau demonstrates that the Artisan is aware that Adenovirus has been utilized in separation processes.

Applicant argues that the Zhang declaration made of record 3/2/06, paragraphs 11-12, demonstrate that the RSV is so distinct from Adenovirus, being more fragile with regard to salt levels, that the Artisan would not understand that ultrafiltration would work for adenovirus (pp. 27-28, paragraph bridging).

Such is not persuasive. First, if the Adenovirus is more refractory to tonicity, any method which utilizes tonicity would be even more expected to work for Adenovirus. Second, the tonicity is not effected by ultrafiltration, and hence, the Argument is completely misplaced. Third, the Argument fails to even connect the dots, and hence, the Examiner does not even know for certain if such is what Applicant is trying to argue. Hand-waving is not enough to overcome a rejection.

Applicant argues that Table 10 demonstrates the contaminating NA concentration is "meger[ly]" affected by ultrafiltration, and thus, contrary to the Examiner's argument, Table 10 provides evidence that ultrafiltration would not result in the claimed contaminant levels (p. 28, paragraph 2).

Such is not persuasive. If Applicant's table does not demonstrate the required level of contamination, then it would appear that Applicant has absolutely no support for the claimed level of contamination in the specification. Second, if Applicant is going to formulate the composition purified, the purification step of the claims must encompass such steps of purification, and must therefore yield levels at least at the level required. Third, Table 10 simply does state the level of contamination required.

Conclusion

No Claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/
Examiner of Art Unit 1633